Indian Journal of Chemistry
Vol. 37B, February 1998, pp. 145 - 150

Synthesis, antifungal and antibacterial activities of some new 2-benzylideneamino-5-arylimino-3-oxo-1,2,4-thiadiazolidines

A K Choubey, A K Tripathi & R Singh*
Department of Applied Chemistry, Institute of Technology, Banaras Hindu University, Varanasi 221 005, India

Received 13 March 1997; accepted 15 October 1997

3-Oxo-1,2,4-thiadiazolidines **3a-e** have been proved to be exceptionally promising antifungal and anti-bacterial moieties. Synthesis of this new series of compounds has been achieved by a single pot method, i.e. by the oxidehydrogenation of 1-aryl-5-benzylideneamino-2,4-thiobiurets **1a-e** with *N*-chlorosuccinimide in ethanol medium in 60-65% yields, respectively. Oxidative debenzylation and cyclisation of the related 1-aryl-5-benzylideneamino-2-*S*-benzyliso-2,4-thiobiurets **2a-e** has also been accomplished leading to the formation of the above oxothiadiazolidines **3a-e** in moderate yields.The antifungal activity of **3e** has shown maximum inhibition (100%) against *Colletotrichum* sp. at 500μg/mL. The compounds **3a,c,d** are also the promising candidates which have shown more than 72% inhibition against all the tested fungi. Similarly the compounds **3a** and **3e** at 10 mg/mL concentration has exhibited maximum antibacterial activity by disc diffusion technique against ten listed micro-organisms. Thus the present series of compounds may be further taken up for their futurestic *in vivo* plant cell screening.

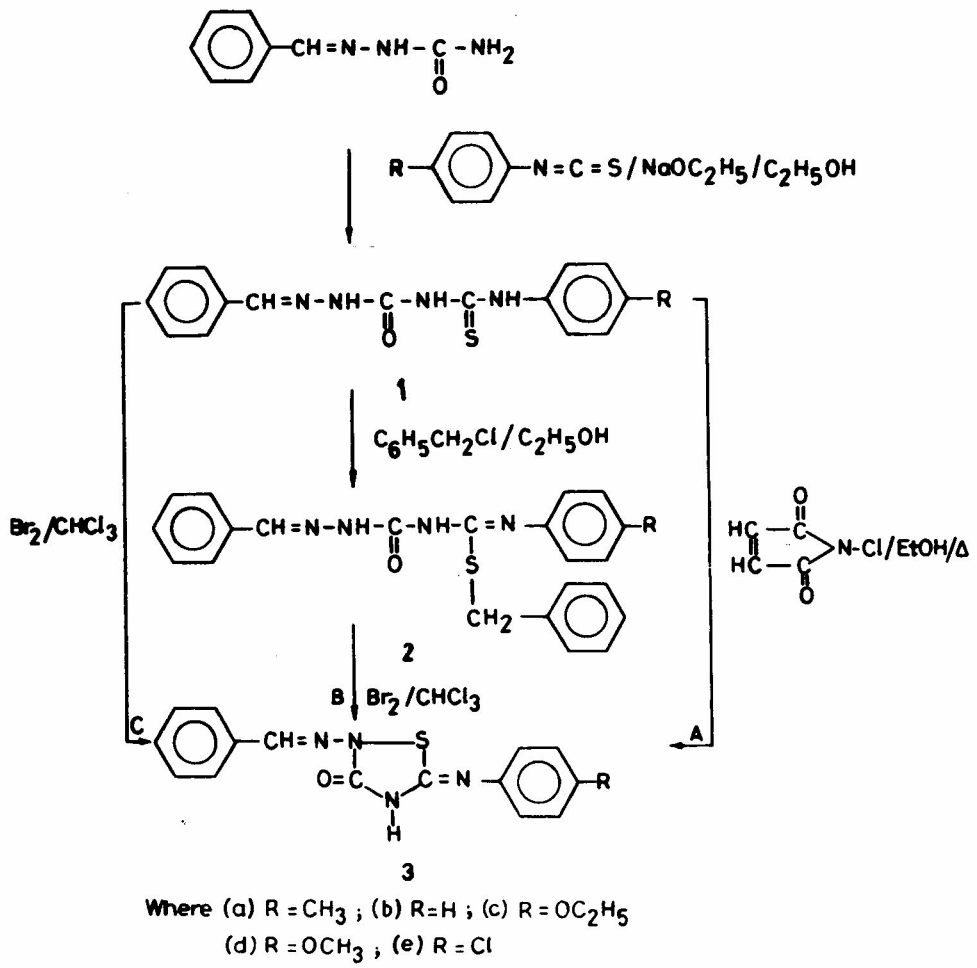
The chemistry of thiazolidinones and thiazolidindiones, the oxo derivatives of tetrahydrothiazole, has drawn considerable attention of a number of investigators due to their varied biological and physiological activities, e.g. antitubercular[1], antibacterial[2], antifungal[3,4], local anaesthetic[5] and radiation protector[6] activities. The oxidative debenzylation and cyclisation[7,8] technique has been reported as a standard technique for the synthesis of N and S containing 1,2,4-thiadiazolidines. Chetia *et al.*[9] have also devised a simpler and novel route to the synthesis of certain 1,2,4-thiadiazolines by the interaction of corresponding substituted thioureas with *N*-chlorosuccinimide.

Keeping in view the above facts and varied biological activities associated with thiadiazolidines, in the present communication, attempts have been made to extend Chetia's[9] single pot method to the synthesis of 2-benzylidine-amino-5-arylimino-3-oxo-1, 2, 4-thiadiazolidines **3** from the related 1-aryl-5-benzylideneamino-2,4-thiobiurets **1** and *N*-chlorosuccini-mide interaction (Method A).

Apart from the above convenient route for the synthesis of **3**, these compounds were also prepared by the oxidative debenzylation and cyclisation of related 1-aryl-5-benzylideneamino-2-*S*-benzyliso-2,4-thiobiurets **2** with molecular bromine (Method B). The compounds **3** were also obtained alternatively by Method-C. The structure of compound **3** was further confirmed by elemental analysis, ^{1}H NMR spectra and undepressed mixed melting point with authentic samples and superimposible IR spectra.

The sequence of reaction mechanism of Method-A has been depicted in Scheme I.

It appears that during the interaction of *N*-chlorosuccinimide with 1-aryl-5-benzylidene-amino-2,4-thiobiurets **1**, the chloro group attaches to the sulfur of the thiobiuret and forms 1-aryl-5-benzylidine-amino-2-*S*-chloroiso-2,4-thiobiuret as an unstable intermediate **2** in the transition state. The lone pair of electrons present on the adjoining nitrogen atom of **2** nucleophilically attacks the sulfur atom and gets converted into another unstable 2-benzylideneamino-5-arylimino-3-oxo-1, 2, 4-thiadiazolidonium intermediate **3**, which



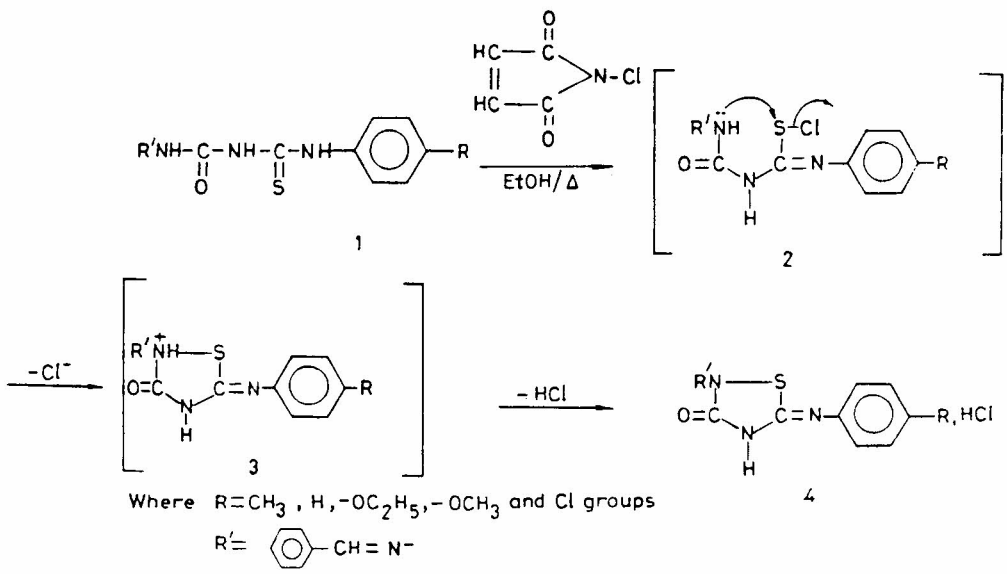
Where (a) R = CH_3 ; (b) R=H ; (c) R = OC_2H_5
(d) R = OCH_3 , (e) R = Cl

Scheme I

simultaneously liberates a proton and affords a stable 2-benzylideneamino-5-arylimino-3-oxo-1, 2, 4-thiadiazolidine hydrochloride **4**. The probable reaction mechanism is shown in Scheme II.

Antifungal activity

Compounds **3a-e** were screened for their fungicidal activity by glass slides method[10] against ten typical pathogenic agricultural fungi, namely, *Alternatia alternata, A. tenuissima, Aspergillus niger, Curvularia lanata, Colletotrichum* sp., *Fusarium ceceri, F. udum, Monilia* sp., *Trichoderma* sp. and *Ustilago* sp. which cause serious plant diseases in India. The effect of these compounds on the spore germination of plant pathogenic fungi were carried out at different concentration (100, 300 and 500 μg/mL) at 25±2°C for 24 hr of incubation. Each tested compound has shown maximum inhibition only at 500 μg/mL. Amongst the compounds tested for potential fungicidal activity by spore germination method, the compound **3e** having chloro group at *p*-position was found to show complete inhibitory effect (100%) against *Colletotrichum* sp. at 500 μg/mL concentration. This compound also showed maximum inhibitory effect against all the fungi, i.e. > 85%. The compound **3c**, with aryl group as *p*-ethoxyphenyl has attributed remarkable inhibitory effect (97.20%) against *Fusarium ceceri*. However, all the fungi have exhibited more than 89% inhibition on the same concentration. The compound **3d** with aryl group as *p*-methoxyphenyl showed maximum inhibitory effect (94.05%) in the case of *Ustilago* sp. Almost similar effects (90.88% and 90.71%) were discerned in *Fusarium udum* and *Alternaria tenuissima* spores at the aforesaid concentration while in the case of other fungi the inhibition was



Scheme II

more than 88%. The other title compound **3a**, containing *p*-methylphenyl group attributed the maximum inhibition (88.92%) against *Colletotrichum* sp. Almost similar effect (86.31% and 85.34% inhibition) was seen in the case of *Monilia* sp. and *Aspergillus niger* spores. About 72-85% inhibitory effect was observed against other fungi. The compound **3b** has shown negligible amount of inhibition against all the fungi and maximum inhibitory effect (29.66%) was seen in the case of *Curvularia laneta* only. On the basis of aforesaid observation, it is therefore, concluded that the order of inhibitory effect against all the tested fungi is influenced by the type of substitution at *para*-position i.e. chloro > ethoxy > methoxy > methyl and when there is no substitution at *para*-position the inhibition is almost minimal. These results indicate the possible use of these compounds for fungal plant disease control. However, the effect(s) of these compounds on host plant and their mode of action on targated organism still remains to be studied.

Antibacterial activity

Antibacterial activity of 2-benzylideneamino-5-arylimino-3-oxo-1,2,4-thiadiazolidines **3a-e** at 10 mg/mL concentration was performed by Disc diffusion technique[11] against ten known bacterial strains namely, *Escherichia coli, Klebsiella pneumoniae, Proteus vulgaris, Shigella flexneri, Salmonella typhimurium, Enterococcus faecalis, Staphylococcus aureus, Pseudomonas aeruginosa, Vibrio cholerae* 01 and *Vibrio cholerae* 0139 respectively. It is concluded from the screening results that the related thiadiazolidines are most effective against all micro-organisms at the given concentration when aryl group is a *p*-methylphenyl **3a** and *p*-chlorophenyl **3e**. Besides these, the other derivatives are also effective against a few selected micro-organisms. Phenyl derivative is effective against *Staphylococcus aureus* and *Vibrio cholerae* 0139 whereas *p*-ethoxyphenyl derivative shows positive response against *Vibrio cholerae* 0139. Almost similar effect was seen in *Escherichia coli* and *Staphylococcus aureus* in case of *p*-methoxyphenyl group. Among the compounds screened for antibacterial activity, the compounds **3a** and **3e** have shown remarkable antibacterial effect even at very low concentrations. These results indicate that these compounds may be used as control measures against different infections. However, the effects of these compounds on host cell and their mode of action remains to be studied.

Experimental Section

All the melting points were determined by Kofler hot stage apparatus and are uncorrected. IR spectra were recorded in Nujol on JASCO FT/IR-5300 spectrophotometer and ^{1}H NMR spectra (in DMSO-d_6) on Jeol FX 90 Q spectrometer (90

MHz-instrument). All the precursors were prepared in conformity with the methods described in the literature. The purity of the compounds was confirmed by TLC.

1-(*p*-Methylphenyl)-5-benzylideneamino-2, 4-thiobiuret 1a. General procedure. A solution of benzaldehydesemicarbazone (5 g, 0.03 mole) and *p*-methylphenylisothiocyanate (4.47 g, 0.03 mole) in ethanol (100 mL) was refluxed with sodium ethoxide (2.04 g, 0.03 mole) for 6 hr. On evaporation of the solvent, the semi-solid mass obtained was washed with pet. ether (40-60°C). This on treatment with ethanol, gave a hard granular solid which on crystallisation from ethanol furnished 1-(*p*-methylphenyl)-5-benzylideneamino-2,4-thiobiuret **1a** as a light yellow crystalline product; yield 6.73 g (72%); m.p. 210°C.

Compounds **1b-e** were prepared similarly and their physical data are given in Table I.

1-(*p*-Methylphenyl)-5- benzylideneamino-2*S*-benzyliso-2,4-thiobiuret 2a. General procedure. Compound **1a** (6g, 0.02 mole) in ethanol (100 mL) was refluxed with benzylchloride (2.50 g, 2.26 mL) for 6 hr. The resulting mixture was then basified with cold ammonia solution (15 mL, sp. gr. 0.9 mole). The free base, obtained as a semi-solid mass, was treated with a little ethanol to yield a solid mass, which was filtered under suction. On crystallisation from ethanol **2a** was obtained as a colourless crystalline product, yield 5.55 g (69%); m.p. 219°C.

Compounds **2b-e** were similarly prepared and their physical data are given in Table I.

2-Benzylideneamino-5- (*p*-methylphenylimino)-3-oxo-1,2,4-thiadiazolidine 3a. General procedure

Method-A

A solution containing **1a** (6 g, 0.02 mole) and *N*-chlorosuccinimide (2.66 g, 0.02 mole) in ethanol (100 mL) was heated under reflux for 6 hr. The reaction mixture was then extracted with chloroform and dried over anhydrous calcium chloride. On evaporation of chloroform under vacuum in a rotary evaporator; a solid compound was obtained. On crystallisation from methanol compound **3a** was obtained as a light yellow product, yield 4.28 g (69%); m.p. 200°C.

Table I—Physical data of compound **1** and **2**

Compd	R	Mol. formula (Mol. wt.)	Yield (%)	m.p. °C	Found (%) (Calcd)			
					C	H	N	S
1a	CH_3	$C_{16}H_{16}N_4SO$ (312)	72	210	61.57 (61.54	5.10 5.13	17.91 17.95	10.20 10.26)
1b	H	$C_{15}H_{14}N_4SO$ (298)	76	260	60.36 (60.40	4.68 4.70	18.83 18.79	— —)
1c	OC_2H_5	$C_{17}H_{18}N_4SO_2$ (342)	69	265	— (—	— —	16.35 16.37	9.40 9.36)
1d	OCH_3	$C_{16}H_{16}N_4SO_2$ (328)	71	202	58.59 (58.54	4.90 4.88	17.00 17.07	— —)
1e	Cl	$C_{15}H_{13}N_4SOCl$ (332.5)	72	258	— (—	— —	16.81 16.84	9.59 9.65)
2a	CH_3	$C_{23}H_{22}N_4SO$ (402)	69	219	— (—	— —	13.90 13.93	7.93 7.96)
2b	H	$C_{22}H_{20}N_4SO$ (388)	66	213	68.00 (68.04	5.20 5.15	14.46 14.43	— —)
2c	OC_2H_5	$C_{24}H_{24}N_4SO_2$ (432)	62	92	— (—	— —	13.00 12.96	7.46 7.41)
2d	OCH_3	$C_{23}H_{22}N_4SO_2$ (418)	64	216	66.00 (66.03	5.20 5.26	13.42 13.40	— —)
2e	Cl	$C_{22}H_{19}N_4SOCl$ (422.5)	54	202	— (—	— —	13.28 13.25	7.57 7.57)

Table II -Characterization data of compounds 3a-e

Compd	R	Mol. formula (Mol. wt.)	Yield (%)	m.p. °C	EIMS m/z	Found (%) (Calcd)				^{1}H NMR (DMSO)
						C	H	N	S	
3a	CH_3	$C_{16}H_{14}N_4SO$ (310)	65	200	310 (M^+)	62.00 (61.94)	4.55 4.52	18.09 18.06	10.37 10.32)	2.51(s,Ar-CH_3), 6.7(s,-NH, D_2O exchangeable), 7.31(m,9Ph,H_x), 7.82(s, -CH=N)
3b	H	$C_{15}H_{12}N_4SO$ (296)	62	205	296 (M^+)	60.89 (60.81	4.10 4.05	18.94 18.90	— —)	6.43(s,-NH, D_2O exchangeable), 7.32(m,10Ph, H_x), 7.81(s, -CH=N)
3c	OC_2H_5	$C_{17}H_{16}N_4SO_2$ (340)	65	211	340 (M^+)	— (—	— —	16.49 16.43	9.49 9.41)	1.25(t,CH_3), 4.16(q,CH_2), 6.33(s,-NH, D_2O exchangeable), 7.32(m,9Ph,H_x), 7.81(s, -CH=N)
3d	OCH_3	$C_{16}H_{15}N_4SO_2$ (327)	63	208	327 (M^+)	58.69 (58.72	4.63 4.59	17.11 17.13	— —)	3.81(s,-OCH_3), 6.45(s,-NH, D_2O exchangeable), 7.31(m,9Ph,H_x), 7.80(s, -CH=N)
3e	Cl	$C_{15}H_{11}N_4SOCl$ (330.5)	60	184	330 (M^+)	— (—	— —	16.99 16.94	9.61 9.61)	6.30(s,-NH, D_2O exchangeable), 7.43(m,9Ph,H_x), 7.80(s, -CH=N)

The compounds **3b-e** were prepared similarly and their characterization data are given in Table II.

Method-B

Compound **2a**(4g, 0.01 mole) was moistened with chloroform and was treated with molecular bromine until the colour of bromine persisted. The reaction mixture was warmed up considerably evolving lachrymatory fumes of benzylbromide. After rubbing the reaction mixture for 1 hr, the semi-solid product was washed with ether (20 mL×3) and on trituration with ethanol afforded the hydrobromide of **3a** which on treatment with ammonia solution gave the free base **3a.** It was crystallised from methanol; yield 2.01 g (65%); m.p. 200°C.

Compounds **2b-e** were similarly oxidatively debenzylated to afford **3b-e**, which were found to be identical with compounds obtained by Method - A (Table II).

Method-C

Compound **1a** (3.12g, 0.01 mole) was oxidised with a solution of bromine in chloroform. Addition of ether afforded the corresponding hydrobromide, which on basification with ammonia solution yielded the free base **3a**. It was crystallised from methanol; yield 1.89 g (61%); m.p. 200°C.

Compounds **1b-e** were similarly oxidised to give **3b-e**, which were shown to be identical to compounds reported in Table II.

Acknowledgement

The authors are thankful to Prof. V K Verma, Head, Department of Applied Chemistry, Institute of Technology, Banaras Hindu University, for discussion and laboratory facilities.

References

1 Kobzina I W, *US Patent*, **1982**, 4309209; *Chem Abstr*, **1982**, 157398.
2 Zumach G, Holtschmidt H & Engelbert K, *German Patent (DBP)*, 1970, 1907116, *Chem Abstr*, 73, **1970**, 98957.
3 Weuffen W, Pyl T, Gruebner W & Juelich W D, *Pharmazie*, 20, **1965**, 629, *Chem Abstr*, 64, **1966**, 5488.
4 Ali MR, Singh R & Verma V K, *Indian J Chem*, 24B, **1985**, 977.
5 Bhargawa P N & Chourasia M R, *J Pharm Sci*, 58, **1969**, 896.

6 Yu T, Yuchenok II', Frigidova L M & Shadurskii K S, *Farmacol Toksikol*, 43, **1980**, 725; *Chem Abstr*, 94, **1981**, 57964n.

7 Ali M R & Verma V K, *Synthesis*, **1985**, 691.

8 Pandey A K, Singh R & Verma V K, *Indian J Chem*, 24B, **1985**, 977.

9 Chetia J P, Mazumdar S N & Mahajan H P, *Synthesis*, **1985**, 83.

10 Committee on Standardization of Fungicidal Tests. The American Phytopathological Society, 'The Slides Germination Method of Evaluating Protectant Fungicides', *Phytopathology*, 33, **1943**, 627.

11 Bauer A W, Kirby W M M & Sherris J C, *Am J Chemical Pathology*, 45, **1966**, 493.